

Fetal MCA Doppler to time intrauterine transfusions in red cell alloimmunisation:

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TITLE: Fetal MCA Doppler to time intrauterine transfusions in red cell allo-immunisation: A randomised trial.

SHORT TITLE: MCA Doppler to time IUTs

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Objectives: Red cell alloimmunisation affects up to 0.6% of all live births, and can be successfully treated with intrauterine fetal blood transfusion. Fetal middle cerebral artery (MCA) Doppler peak systolic velocity (PSV) is a non-invasive test, to identify fetal anaemia and requiring intrauterine transfusion (IUT). Traditionally, timing of subsequent IUTs has involved estimating a fall in fetal haematocrit of 1% per day, or a fall in fetal haemoglobin of 0.3g/dL per day.

We conducted a pragmatic multi-centre randomised trial to evaluate whether Doppler MCA-PSV in the fetus that has undergone one IUT for anaemia secondary to red cell alloimmunisation was non-inferior to timing IUT by timing based on predicting the fall in fetal haematocrit or fetal haemoglobin, without compromising infant haemoglobin at birth.

Methods: We conducted an international, multi-centre randomised trial.

Women with pregnancies complicated by fetal anaemia secondary to red cell alloimmunisation (due to any antibody alone or in combination) as indicated by the need to undergo a single IUT were eligible for inclusion.

Women were randomised to the ***Timing of Transfusion by MCA-PSV Group*** (ultrasound determination of the fetal MCA-PSV, with a serial upward trend with values >1.5MoM considered indicative of the need for another IUT), or to the ***Timing of Transfusion by Prediction of the Fall in Fetal Haematocrit (Hct) Group*** (subsequent IUT's timed according an estimated fall in fetal Hct of 1% per day or fetal haemoglobin of 0.3g/dL per day, to maintain the fetal haemoglobin between 7-10g/dL).

The primary study outcome was infant haemoglobin measured at birth.

The trial was registered on the Australian and New Zealand Clinical Trials Register (ACTRN12608000643370).

Results: We randomised 71 women (36 to the MCA-PSV Group; and 35 to the Fall in Fetal Hct. Group) from 13 centers in Australia, New Zealand, Canada, United Kingdom, Ireland, Belgium, and Argentina.

The median gestational age at randomization was 30.3 weeks, and the majority of women were Caucasian and non-smokers; 9.9% of women had Kell alloimmunisation, and 14% of fetuses were hydropic at their first IUT.

There were no statistically significant differences between the two treatment groups with regards to mean haemoglobin at birth (MCA-PSV Group 103.6 ± 38.2 g/dL versus Fall in Fetal Hct Group 120.3 ± 31.4 g/dL; adjusted mean difference -15.6; 95% CI -32.4 to 1.3; $p=0.070$), or the number of IUTs performed after randomisation (MCA-PSV Group 1.75 (± 1.79) versus Fall in Fetal Hct Group 1.80 (± 1.32); adjusted relative risk aRR 0.88; 95% confidence interval (CI) 0.61 to 1.26; $p=0.474$). There were no statistically significant differences between the two groups in the risk of adverse infant outcomes related to alloimmunisation, or procedure related complications.

Conclusions: Both Doppler MCA-PSV measurement and estimating the fall in fetal haematocrit or haemoglobin can be used to time second and subsequent IUTs.

INTRODUCTION:

Middle cerebral artery (MCA) Doppler peak systolic velocity (PSV) identifies the fetus at risk of anaemia and requiring intrauterine transfusion (IUT).¹ Originally described by Mari,² a PSV above 1.5 multiples of the median (MoM) identified moderate or severe fetal anaemia with sensitivity 100%, and false positive rate (FPR) 12%.^{2, 3} Despite limitations,⁴ MCA-PSV is widely used, compares favourably with amniotic fluid bilirubin concentrations,⁵ and has largely replaced serial amniocentesis in managing red cell alloimmunisation.

Traditionally, timing of subsequent IUTs involves estimating the rate of red cell destruction,⁶⁻⁸ either by fall in fetal haematocrit,⁹ or haemoglobin.¹⁰ Correction of fetal anaemia following IUT normalises fetal MCA-PSV measurements,¹¹ extending potential use to time second and subsequent procedures.^{10, 12-15} However, as highlighted by Moise, this is not supported by available data.¹⁶

Deti and colleagues¹³ used a MCA-PSV >1.69MoM to correctly identify all fetuses with severe anaemia following a single IUT, with a false positive rate of 6%. However, following two or more IUTs, MCA-PSV values above 1.5MoM have variably identified severe fetal anaemia with sensitivity between 84 and 100%,^{10, 14, 15} with false positive rates of the order of 50%.^{10, 15} Indeed, a recent study has indicated that, particularly after second IUTs, formulae to estimate red cell destruction are more accurate than MCA-PSV.¹⁷

We conducted a pragmatic trial to evaluate whether timing of second and subsequent IUTs with Doppler MCA-PSV was non-inferior to estimating the fall in fetal haematocrit or haemoglobin, without compromising haemoglobin at birth.

METHODS:

Study Design: A multi-centre, randomised controlled trial.

Inclusion Criteria: Women with a singleton pregnancy complicated by fetal anaemia secondary to red cell alloimmunisation from any red cell antibody as indicated by the need to have performed a single IUT were eligible to participate.

Exclusion Criteria: Pregnant women whose fetus had anaemia secondary to any other cause, or with known chromosomal anomalies were ineligible.

Trial Entry: Eligible women were identified after the decision was made to proceed with the first IUT, and provided written informed consent to participate.

Randomisation: We used an on-line randomisation service with computer generated schedule using balanced variable blocks, and stratification for the presence or absence of hydrops at first IUT, type of antibody (Kell versus other), and centre of birth. Women were randomized to *Timing of Transfusion by MCA-PSV Group* (with a serial upward trend and MCA-PSV values $>1.5\text{MoM}$ indicative of the need for another IUT), or to the *Timing of Transfusion by Estimating the Fall in Fetal Hct Group* (subsequent IUT's timed according an estimated fall in fetal Hct of 1% per day).

Treatment Schedules:

Timing of Transfusion by MCA-PSV Group - Women underwent serial ultrasound examinations performed in a standard fashion³ and at a frequency determined by

individual clinicians experienced in the management of fetal alloimmunisation. In short, measurements were made in the absence of fetal breathing movements, with the woman in a semi-recumbent position. An axial section was obtained through the fetal brain, caudal to the level required for the measurement of the biparietal diameter, with identification of the middle cerebral artery using colour or power Doppler settings, and angle of insonation of 0-10 degrees. Angle correction did not exceed 30 degrees. The sample volume was placed near the internal carotid artery, and a measurement of the peak Doppler waveform taken after obtaining five representative waveforms. Consistent with practices within each participating fetal medicine unit, the MCA-PSV value was recorded on standardised, and an upward serial trend in values consistently >1.50MoM considered indicative of the need for IUT. The new identification of ascites and/or hydrops was additionally considered indicative of the need for IUT, regardless of the MCA-PSV value.

Timing of Transfusion by Estimation of the Fall in Fetal Hct Group - Women had the timing of IUTs planned using standard criteria to predict the rate of red cell destruction and development of anaemia, based on gestational age, haemoglobin prior to IUT, and haemoglobin at IUT completion.⁶⁻⁸ A fall in fetal haematocrit of 1% per day,⁹ or fetal haemoglobin of 0.3g/dL per day, was estimated, with IUT undertaken according to the usual practices within each center, to maintain the fetal haemoglobin between 7-10g/dL.¹⁰

Both treatment groups:

At a gestation beyond 24 weeks, women were administered antenatal corticosteroids for fetal lung maturation.^{1, 18} Blood transfused was fresh, matched to the woman's

blood group, CMV negative, and irradiated, with haematocrit between 75-80%. IUTs were performed under ultrasound guidance by appropriately trained staff.¹ The site of transfusion (umbilical cord, intrahepatic vein, or intra-peritoneal), and use of fetal paralysis was at the discretion of individual clinicians, in accordance with individual and institutional practices.^{1, 19, 20} The transfused blood volume was determined considering gestational age, estimated fetal weight, and pre-transfusion hemoglobin,^{1, 21} with a post transfusion specimen obtained where possible. The target post transfusion haemoglobin was a deficit of 4g/dL below the mean for gestational age.^{6, 7} Following the procedure, monitoring of the fetal heart rate and uterine activity were undertaken.

Decisions relating to the timing of last IUT and of optimal timing of birth for women with red cell alloimmunisation are uncertain, with recommendations for birth ranging from after 32 weeks²² to 36²³ or 38 weeks gestation.¹ In the context of this pragmatic trial, these decisions were made following discussion between the woman and her caregivers. At birth, a cord blood sample was taken to estimate haemoglobin, and/or haematocrit. Clinical outcomes were abstracted from case notes after birth. The woman and her caregivers were not blinded to treatment allocation, although where possible, staff assessing outcomes were blind to treatment allocation.

Outcomes

The primary outcome was infant cord blood haemoglobin at birth.

A range of secondary outcomes included:

1. Adverse infant outcomes related to alloimmunisation (one or more of stillbirth (intrauterine fetal death after trial entry and prior to birth); neonatal death (death of a live-born infant before 28 days of age); severe fetal anaemia (at the time of second or any subsequent transfusion, defined as pre-transfusion haemoglobin \geq 5 standard deviations below the mean for gestational age, with the mean Hb for gestational age defined according to the following formula:

$$\text{Mean Hb} = 11 + (GA_{\text{weeks}} - 17) \times 0.19$$
);⁶ severe anaemia at birth (haemoglobin \geq 5 standard deviations below the mean for gestational age); or neonatal exchange transfusion).
2. Procedure related complications necessitating emergency birth (including one or more of the following within one week of the procedure: preterm pre-labour ruptured membranes (PPROM); preterm labour; chorioamnionitis; placental abruption or antepartum haemorrhage).
3. Infant complications related to alloimmunisation (including preterm birth before 34 weeks gestation; jaundice requiring treatment; admission to the neonatal intensive care unit; neonatal top-up transfusion).
4. Maternal complications including antepartum haemorrhage or abruption; preterm premature rupture membranes; threatened preterm labour; chorioamnionitis.
5. Number of IUTs after randomisation.

Sample Size

The sample size and primary outcome were modified prior to finalising trial data, and before any of the planned analyses were performed, to account for slower than anticipated recruitment, and to be reflective of the available funding. Assuming a standard deviation in infant haemoglobin of 1g/dL, a sample of 35 participants per

group (70 in total) provides 80% power (two-sided $\alpha=0.05$) to detect non-inferiority with a non-inferiority margin of 0.6 g/dL.

The original sample size was 536 women, to detect a 30% reduction in a primary composite adverse outcome (stillbirth, neonatal death, severe fetal anaemia, severe anaemia at birth, neonatal exchange transfusion), with 5% significance level, and 90% power.

Analysis and Reporting of Results

Analyses used an intention-to-treat approach. Baseline characteristics of women were examined as an indication of comparable treatment groups, and included maternal age, race, height, weight, smoking history, past obstetric history (including previous alloimmunised pregnancy; past preterm birth or perinatal loss related to alloimmunisation). No imputation was performed for missing data.

The effect of treatment was estimated using linear regression models for continuous outcomes, log binomial regression for binary outcomes, and log Poisson regression for count outcomes. Estimates are difference in means (MCA-PSV – Fall in Haematocrit), relative risk (MCA-PSV/Fall in Haematocrit) and rate ratio (MCA-PSV/Fall in Haematocrit) respectively, along with 95% confidence intervals. For number of transfusions, an offset was included for number of days between randomization and delivery.

Both unadjusted and adjusted analyses were performed, adjusted analyses including the stratification variables presence of hydrops and antibody type (Kell vs other) as covariates. A small number of events were observed for many outcomes, which led to

convergence issues with the models. Where there were too few events to allow for adjustment, only unadjusted analyses were performed; where there were too few events for any modelling, a Fishers Exact test was performed.

Trial Registration

The trial was registered on the Australian and New Zealand Clinical Trials Register (ACTRN12608000643370).

RESULTS:

Between October 2009 and October 2013, 75 women were recruited. One woman had 3 affected pregnancies, with data pertaining to the first randomisation only included, and two women were randomised in error. A total of 71 women were randomised, 36 to the **MCA-PSV Group**, and 35 to the **Fall in Fetal Hct Group** (Figure 1). Baseline characteristics were similar between the two randomised groups (Table 1). The mean age of participating women was 33.6 years (\pm 4.7years), and gestational age at randomisation 30.3 weeks (interquartile range (IQR) 27.7 to 32.00). Overall 60.6% of participants were Caucasian, and 25.4% were Hispanic. Most women were non-smokers (85.9%), had no evidence of fetal hydrops at first IUT (85.9%), with alloimmunisation antibodies other than Kell (90.1%).

There was one stillbirth (Fall in Fetal Hct Group) in a fetus with hydrops at 31 weeks, which occurred between randomization and the scheduled second IUT, and 5 neonatal deaths (3 in the MCA-PSV group and 2 in the Fall in Fetal Hct group). Two infants in the MCA-PSV Group had hydrops and died following preterm birth, within the week following first IUT (29, and 30 weeks respectively), due to complications of prematurity. The third infant was born at 33 weeks gestation and died secondary to liver failure following multiple exchange and top-up transfusions in the postnatal period, and severe respiratory distress syndrome. One infant in the Fall in Fetal Hct Group required 5 IUTs, but died following preterm birth, and within one week of the last IUT at 28 weeks gestation. The infant's haemoglobin at birth was 97g/dL, and complications of prematurity were compounded by an undiagnosed complex congenital cardiac lesion. The second infant was born at 33 weeks gestation within a

week of the second IUT. Complications of prematurity were compounded by sepsis and multi-organ failure.

There were no statistically significant differences between the two treatment groups with regards to mean haemoglobin (MCA-PSV Group 103.6 ± 38.2 g/dL versus Fall in Fetal Hct Group 120.3 ± 31.4 g/dL; adjusted mean difference (aMD) -15.6; 95% CI -32.4 to 1.3; $p=0.070$), or mean number of IUTs after randomisation (MCA-PSV Group $1.75 (\pm 1.79)$ versus Fall in Fetal Hct Group $1.80 (\pm 1.32)$; adjusted relative risk aRR 0.88; 95% confidence interval (CI) 0.61 to 1.26; $p=0.474$) (Table 2). There were no statistically significant differences in gestational age at birth (MCA-PSV Group 35.23 ± 2.30 weeks versus Fall in Fetal Hct Group 35.07 ± 2.28 weeks; aMD 0.26; 95% CI -0.75 to 1.27; $p=0.613$); preterm birth before 34 weeks (MCA-PSV Group 9/36 (25.00%) versus Fall in Fetal Hct Group 7/35 (20.00%); aRR 1.36; 95% CI 0.61 to 3.05; $p=0.458$); or birth weight (MCA-PSV Group 2581.11 ± 604.03 g versus Fall in Fetal Hct Group 2602.69 ± 591.34 g; aMD -49.79; 95% CI -246.14 to 146.57; $p=0.619$). While a high proportion of infants were admitted to the neonatal unit, (MCA-PSV Group 28/35 (80.00%) versus Fall in Fetal Hct Group 22/34 (67.65%); aRR 1.20; 95% CI 0.89 to 1.60; $p=0.231$), there were no statistically significant differences in exchange transfusion (MCA-PSV Group 14/35 (40.00%) versus Fall in Fetal Hct Group 9/34 (26.47%); aRR 1.42; 95% CI 0.71 to 2.83; $p=0.316$); top-up transfusion (MCA-PSV Group 21/35 (60.00%) versus Fall in Fetal Hct Group 19/34 (55.88%); aRR 1.05; 95% CI 0.70 to 1.57; $p=0.827$); or jaundice requiring treatment MCA-PSV Group 29/34 (85.29%) versus Fall in Fetal Hct Group 30/34 (88.24%); aRR 1.06; 95% CI 0.91 to 1.22; $p=0.460$) (Table 2).

There were no statistically significant differences in procedure related or maternal complications (Table 3).

There was no evidence to suggest that outcomes varied according to the presence of hydrops at first IUT, or the responsible antibody (data not shown).

DISCUSSION:

Principal Findings

Doppler MCA-PSV measurement is not inferior to estimating the fall in fetal haematocrit to time second and subsequent IUTs, although infants born following Doppler MCA-PSV to time IUTs had a non-statistically significant trend towards lower mean haemoglobin at birth (103.6g/dL vs 120.3g/dL), and more frequent need for neonatal exchange transfusion (40.0% vs 26.5%). There were no significant differences identified with regards to other alloimmunisation or procedure related complications.

Comparisons with other studies

The procedure related complication risk in our trial was 2.8%, with an overall survival rate of 93%, both of which are consistent with the 3.1%, and greater than 90%, respectively reported in the literature.²⁰ In contrast, Zwiers and colleagues have recently reported their extensive 27-year experience involving almost 1,700 transfusion procedures, from a single tertiary referral center.²⁴ In this cohort, survival improved from approximately 89% to 97%, and procedure related complications declined from 3.4% to 1.2% for the time periods 1998-2001 and 2001-2014 respectively. These high survival rates and low complication rates²⁴ are likely the “best case scenario”, reflective of both clinician experience and volume of procedures undertaken, as compared with the necessity of our more pragmatic study design.

Approximately 25% of infants in our trial had severe anaemia at birth, with 85% receiving phototherapy for treatment of jaundice. One third of infants received at least one exchange transfusion, and 60% at least one top-up transfusion. Infants in the

MCA-PSV group tended to a lower haemoglobin at birth and were more likely to receive exchange transfusion, when compared with estimating the fall in fetal haematocrit / haemoglobin. While these differences were not statistically significant, likely reflecting the sample size, they are clinically significant in neonatal care.

Neonatal outcomes reported from our trial are not directly comparable with other study populations reported in the literature. All infants in our trial population required at least one IUT, in contrast to other reports, where outcome comparisons have largely reflected the presence or absence of an antenatal transfusion procedure. Van Kamp reported neonatal outcomes for 191 infants born after any IUT.²⁵ While the mean haemoglobin reported at birth was consistent with our findings, it is difficult to compare other outcomes, with the median number of exchange and top-up transfusions reported, rather than an indication of the number of infants requiring this treatment.²⁵

A study from the United Kingdom followed 28 women with MCA-PSV.²⁶ Reported neonatal complication rates were lower than identified in our trial with 36% of infants requiring phototherapy for jaundice, 25% an exchange transfusion, and 14% a top-up transfusion.²⁶ DeBoer and colleagues have reported outcomes for 89 infants with Rhesus haemolytic disease, where 52 infants required an IUT.²⁷ In this series, while 71% of infants who required an IUT also received an exchange transfusion, they required less phototherapy, but more top-up transfusions, when compared with infants who were not treated in the antenatal period,²⁷ although again, the comparator was infants who did not require an IUT.

Strengths & Weaknesses

To our knowledge, this is the first randomized trial evaluating Doppler MCA-PSV to time second and subsequent IUTs for red cell alloimmunisation. We utilized robust methodology, pre-specified relevant maternal and infant outcomes, and followed a pre-specified analysis plan.

While the primary outcome and sample size was modified from the original trial registration, this occurred prior to finalising data collection, before undertaking any pre-specified analyses, and was made after accounting for slower than anticipated recruitment and the final allocated funding. The trial is adequately powered to identify relatively small differences in haemoglobin concentration at birth between the two treatment practices, but not differences in less common clinical outcomes.

We encountered several barriers in conducting this trial, reflecting the need to involve multiple centres internationally to study a relatively uncommon condition. We experienced considerable delays in commencing recruitment, with the mean time to obtain ethical approval in centres where recruitment occurred being 305 days (range 92 to 608 days). This delay was greater in centres where the ethical approval process was commenced, but where recruitment did not occur (mean 518 days; range 153 to 1,095 days). Many clinical collaborators indicated that time pressures and a lack of research support hampered their participation, although provision of dedicated research support at each site was not possible with only modest financial reimbursement provided per participant recruited. Unfortunately, there were considerable time delays between investigators providing agreement to participate and securing funding. Over this time there was a shift in clinical equipoise, such that

many large referral centres internationally routinely used MCA-PSV to time second and subsequent IUTs, and were therefore no longer willing to participate.

Conclusions

Our findings indicate that both Doppler MCA-PSV measurement and estimating the fall in fetal haematocrit or haemoglobin can be used to time second and subsequent IUTs. However, the trend towards lower infant haemoglobin, increased need for exchange transfusion, and the increased frequency of visits for ultrasound surveillance associated with MCA-PSV Doppler assessment, have resource implications for the woman, and healthcare facility, and are valid considerations in determining the most appropriate method to time IUTs.

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Each author fulfils the requirements for authorship and in particular all have been involved in the development and design of the trial, the conduct of the trial, drafting of the manuscript and revision for intellectual content, and gives approval of the final submitted version. JMD is the data custodian and accepts responsibility for the integrity of the trial and the data analyses. JMD and JL conducted the statistical analyses.

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The authors report no conflict of interest.

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